REMARKS

Claim Amendments

In the interests of expediting prosecution, Applicants have cancelled claims 1-18 without prejudice or disclaimer, so as to focus on the elected species invention as in claims 19-20. Applicants specifically preserve the right to file a continuing/divisional application directed to the cancelled claims.

Species Election

The Examiner has called for a Species Election in item 3 on page 2 of the Office Action. Applicants elect:

A. A variant which binds CD20. Pending claims readable on the elected species are claims 19-20.

B. A method for treating lymphoma. Pending claims readable on the elected species are claims 19-20.

Applicants note that the prior art search has been extended to include all species (item 5, on page 4 of the Office Action).

Section 102(e)

The Examiner rejects claims 1, 3, 4, 8-11, 14 and 15-20 under 35 USC Section 102(e) as being anticipated by US Patent No. 6,528,624 ("the '624 patent"). The Examiner states that the '624 patent claims priority to an additional provisional application filed 4/2/1998 "that has support for the teachings of making antibody variants comprising a human IgG Fc region with amino acid modification in Fc regions including positions at **334** (see entire document, particularly **Table 2 on column 41**) which, in turn, provide sufficient support for relying on the '624 patent as 102(e)." (emphasis added)

Applicants disagree with the Examiner's finding as to what the '624 patent discloses. **Table 2 in column 41** of the '624 patent refers to **E318A**, **K320A**, **K322A**, **P329A**, and **P331A** mutants, not position 334 variant(s). If it is the reference to K334A in column 4, line 52 of the '624 to which the Examiner refers, Applicants note that there the '624 patent explains that such substitution "had little or no effect on C1q binding or complement activation" (lines 51-55 in column 40). Instead, Example 2 in the '624 patent concludes that "the C1q binding epicenter of human IgG1 is centered around K322, P329 and P331" (column 41, lines 16-18).

Reconsideration and withdrawal of the Section 102(e) rejection is respectfully requested.

Section 112, first paragraph, enablement

Claims 1, 3-11, 14, and 15-20 stand rejected under 35 USC Section 112, first paragraph as failing to comply with the enablement requirement.

First, the Examiner contends that "the instant invention is not limited to more effective ADCC in patients or in vitro."

Second, the Examiner asserts that "even in the cases that the host effector mechanisms to monoclonal antibody activity (e.g. Herceptin) are evaluated in vivo, the results often cannot simply be used to predict clinical efficacy because monoclonal antibodies behave differently in different experimental systems, thus even the data from in vivo animal experiments do not translate to therapeutic effect in heterogenous human cancer patients." Eccles *et al.* (2001) and Tutt *et al.* (1998) are cited to support this proposition.

Third, the Examiner contends that "the specification does not reasonably provide enablement for methods of treating <u>any</u> disorder by administering the antibody variants."

Applicants address each of these stated bases of the rejection insofar as they may be considered to apply to claims 19-20 herein.

As to the first basis of the rejection, Applicants note that claim 19 herein recites that the "variant mediates antibody-dependent cell-mediated cytotoxicity (ADCC) in the presence of human effector cells more effectively than the parent antibody," hence, Applicants disagree with the first basis of the rejection.

As to the second basis of the rejection, Applicants submit that the specification enables claim 19 directed to a method for treating lymphoma or leukemia in a mammal comprising administering to the mammal a therapeutically effective amount of the claimed CD20 antibody variant. In this regard, Applicants point out first that CD20 antibodies have been shown to be therapeutically effective for therapy of both lymphoma and leukemia as recited in claim 19. See, for example, page 86 of Eccles *et al.* (2001), cited in the rejection, which discusses CD20 antibody therapy of lymphoma. See, also, WO 00/27428, Grillo-Lopez and White, copy attached, which teaches CD20 antibody therapy of leukemia. Moreover, CD20 antibody Fc variants with improved ADCC function, have been indicated to be therapeutically effective in mammals.

See, for example, US2006/0246004 A1, which describes various CD20 antibody Fc variants with improved ADCC function (see Examples 3, 6, and 12-13), including 2H7.v31, 2H7.v511, and 2H7.v114. (Applicants understand that the Examiner is readily able to access a copy of this published US patent publication, but are willing to provide a copy upon request). Such CD20 antibody variants were shown to be effective at B-cell depletion in mammals; see Examples 9,15-16, and 18-19. Since the *in vivo* studies as disclosed in this US patent publication were used to validate the FDA-approved CD20 antibody for therapeutic use, Applicants submit that the skilled person would consider this evidence to show that the claimed invention was enabled according to 35 USC Section 112, first paragraph. As the Examiner is well aware, the Patent Office does not require human clinical data to support a therapeutic method claim. In any event, claim 19 herein concerns therapy of "mammals" rather than "humans." Thus, Applicants submit that the present patent disclosure coupled with the evidence discussed above refutes the Examiner's suggestion that claims 19-20 are not enabled.

Turning now to the Examiner's suggestion that Eccles *et al.* and Tutt *et al.* show that "even in the cases that the host effector mechanisms to monoclonal antibody activity (e.g. Herceptin) are evaluated in vivo, the results often cannot simply be used to predict clinical efficacy because monoclonal antibodies behave differently in different experimental systems, thus even the data from in vivo animal experiments do not translate to therapeutic effect in heterogenous human cancer patients," Applicants respectfully disagree. Indeed, Applicants submit that Eccles *et al.* and Tutt *et al.* support the enablement of the invention set forth in claims 19-20 by confirming that "anti-CD20 mAb is now producing striking results in relapsed, low grade NHL" (page 3176 of Tutt *et al.*) and "the past few years have witnessed the approval by the Food and Drug Administration of the first mAbs for therapy of cancer: Rituxan (and-CD20 for non-Hodgkin's lymphoma and Herceptin [anti-(c-*erb*B-2/HER-2)} for metastatic breast cancer" (page 86 of Eccles *et al.*) Thus, on balance, Applicants submit that these two references support the notion that CD20 antibodies are therapeutically effective. Indeed, the FDA-approved CD20 antibody was first found to be effective at B-cell depletion in animal studies of the type discussed above in which the CD20 antibody variants of the claims herein have likewise shown to be effective.

Thus, Applicants submit that Tutt and Eccles support, rather than refute, the enablement of the presently claimed invention.

As to the Examiner's third basis of the rejection, that the specification does not reasonably provide enablement for methods of treating "any disorder," this is addressed in claim 19, insofar as the specification clearly teaches and enables therapy of both "lymphoma and leukemia" with a CD20 antibody, and Applicants have demonstrated conclusively herein that CD20 antibody variants as disclosed in the present application would be therapeutically effective for these indications.

Reconsideration and withdrawal of the 35 USC Section 112, first paragraph rejection is respectfully requested.

Statement of Related Cases

Applicant asks the Examiner to consider the following US application, patent and publications that are related to the above application:

U.S. Serial No. 11/520,121
US 7,122,637
US 2006/0194291
US 2006/0194957
US 2006/0194954

Respectfully submitted,
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